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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,302	LAW ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 1/5/04, has been entered. Claims 69-93 are pending and under current examination.

Any rejection made of record in the prior Office action, mailed 5/20/03, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Claim Objections

The prior objection of claim 92 is withdrawn in view of Applicants' amendment to the claims.

Claim 93 is objected to for the following reason: the claim recites the method steps of c) and d). There are no steps a) and b). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 69-93 for written description is withdrawn in view of Applicants' amendments to the claims with regard to the recitation of, "conservative amino acid substitution for a wild type tyrosine residue."

The prior rejection of claims 69-75, 79-92 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record advanced.

Applicants' amendments to the claims 69-78 now recite a chimeric mouse comprising a mutant GP IIIa gene, wherein the mutant gene encodes a GP III a protein having a conservative amino acid substitution for a wild-type tyrosine residue in its mutant cytoplasmic domain, wherein the chimeric mouse has reduced or absent phosphorylation of mutant GP IIIa protein, when compared to wild-type GP IIIa protein and methods of using the claimed mouse.

The Examiner concedes that claims 76-78 and 93 provide a phenotype for the claims transgenic mice, thus, a new rejection for these claims appears below. However, the specification fails to provide an enabling disclosure for the amended claims 69-75 and 75-92. Particularly, with regard to claims 69-73, the specification fails to provide teachings or guidance with regard to the phenotype of a chimeric mouse comprising the mutant GP IIIa gene, as now claimed. Furthermore, the Law Exhibit, provided in a prior Response [filed 1/2/02], fails to provide any teachings or guidance with regard to the chimeric mice as claimed. The specification states that chimeric mice were mated with wild-type females, and then the resulting offspring were genotyped for the presence of wild-type or mutant GP IIIa alleles by Southern blotting. These offspring, which were a mix of wild-type, heterozygous and

homozygous animals. The heterozygote animals were then further crossed to produce +/- and -/- animals. The specification and the Law Exhibit provide teachings with regard to mice which were homozygous for the mutant β3 gene, particularly that platelets isolated from β3 -/- mice failed to aggregate when stimulated with 0.05 units ml^{-1} of thrombin, and formed unstable aggregates when stimulated with 0.1 units ml^{-1} of thrombin. See Law Exhibit. However, the specification fails to provide teachings, guidance or any evidence of record for the phenotype of the chimeric mice, as claimed. Furthermore, it would not be predictable that the production of chimeric mice, as the type claimed, would be reproducible, because chimeric mice have a mixture of cells within their genome, for example, wild-type, heterozygous and homozygous knockout GP IIIa expressing platelets. Accordingly, for reasons of record advanced in prior Office actions, the specification fails to provide an enabling disclosure for the claimed chimeric mice because the specification fails to provide a specific phenotype associated with such chimeric mice. Because the specification discloses no phenotype for the claimed chimeric mice, undue experimentation would have been required for one of skill in the art to make and/or use the claimed invention. Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification fails to provide an enabled use for the claimed chimeric mice without a resulting phenotype. Accordingly, the specification fails to provide

teachings or guidance such that those skilled in the art would know how to make and use the full scope of the claimed invention without undue experimentation.

Furthermore, with regard to claims 79-92, the claims are directed to transgenic mice and methods of producing and using such mice. However, the claims fail to provide a specific phenotype for these mice, and it is reiterated that the state of the art of transgenesis is such that it would not that resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. See also the preceding paragraphs and the prior Office actions. Accordingly, the claimed transgenic mice fail to exhibit a particular phenotype, and one of skill in the art would not be able to make and use the full scope of the claimed invention without undue experimentation.

With regard to the phenotype of the claimed mice, Applicants argue that the specification has provided the description of at least two definable and measurable phenotypes in the specification. Firstly, Applicants point to the lack tyrosine phosphorylation, and that Applicants incorporate U.S. Pat. No. 6,210,913, which enables this phenotype by describing at least one method for assessing phosphorylation of tyrosines on β3 integrin. Secondly, Applicants point to a platelet aggregation phenotype. The prior Office action's rejection states that although the specification teaches that the mice of the instant invention will display "non-normal" platelet aggregation, the specification fails to provide specific support for a phenotype of decreased platelet aggregation. Applicants argue that the instant

specification provides support for the phenotype of decreased platelet aggregation, and point to page 16, lines 1-2. See p. 9-10 of the Response.

With regard to claims 72, 79, 83 and the claims dependent therefrom, it is reiterated that the claims fail to provide a phenotype for the chimeric or transgenic mice. As stated in prior Office actions and in the preceding paragraph, the specification fails to provide an enabling disclosure because the specification discloses no phenotype for the claimed chimeric mice, undue experimentation would have been required for one of skill in the art to make and/or use the claimed invention. The specification fails to provide an enabled use for the claimed chimeric mice without a resulting phenotype. Note that with regard to the method claims [claims 83-91], these claims are not enabling because they fail to provide a phenotype for the mice which are generated by the claimed methods. For the reasons of record and those recited in the preceding paragraphs, the generation of transgenic or chimeric mice is not predictable, and thus, it would have required undue experimentation for one of skill to practice the claimed invention.

Accordingly, in view of the quantity of experimentation necessary for the production and methods of use of the claimed transgenic mice and the unpredictable and undeveloped state of the transgenic, and particularly with respect to the unpredictable nature of the phenotypic effect, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claims 76-78 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a transgene, wherein the transgene comprises DNA encoding a mutant GP IIIa (β3) protein having a conservative amino acid substitution for a wild-type tyrosine in its mutant cytoplasmic domain, wherein said transgenic mouse has platelets with reduced or absent phosphorylation of said mutant GP IIIa (β3) protein when compared to a wild-type mouse, does not reasonably provide enablement for a transgenic mouse which expresses a transgene integrated into its genome wherein the transgene comprises DNA encoding a mutant GP IIIa (β3) protein having a conservative amino acid substitution for a wild-type tyrosine in its mutant cytoplasmic domain, wherein said transgenic mouse has reduced or absent phosphorylation of said mutant GP IIIa (β3) protein when compared to a wildtype GP IIIa (β3) protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches the production and use of a transgenic mammal in which the endogenous GP IIIa gene (also known as β3) has been replaced in whole or in part with a mutant GP IIIa gene, where one or both of the two phosphorylatable cytoplasmic tyrosine residues have been replaced with non-tyrosine residues (see p. 1, lines 11-17). The specification teaches that in these mice, platelets will express an altered GP IIIa gene, and cannot undergo tyrosine phosphorylation, either in whole or in part, when compared to their wild-type

counterparts. The specification specifically teaches that the murine GP IIIa gene was isolated and the two tyrosine residues 747 and 759 were mutated to phenylalanine using standard site-directed mutagenesis (see examples 1-2). The specification teaches that the mutated GP IIIa DNA was then subcloned into a targeting vector containing a neomycin resistant cassette, and the neo^r DNA was flanked by FRT recognition sequences (see example 3). The targeting construct was then transfected into murine ES cells and positive clones were identified (see example 4). The ES cells that contained the mutant GP IIIa DNA were then injected into blastocysts and implanted into pseudo-pregnant foster mothers. The male chimeric mice were identified and mated with wild-type females. The heterozygote offspring were then further mated to produce homozygote animals. The specification teaches that the resulting mice are viable and express GP IIB-IIIa on their platelets at similar levels to that seen in normal animals expressing non-mutant GP IIIa (see p. 22, lines 8-12).

The claimed transgenic mice are enabling for the phenotype of reduced or absent phosphorylation of the mutant GP IIIa in their platelets, however, the claimed mice are not enabled for the breadth of the claims, directed to reduced or absent phosphorylation of mutant GP IIIa protein. This is because the specification specifically teaches that tyrosine phosphorylation of the GP IIIa subunit of the platelet integrin Gp IIb-IIIa is dependent upon platelet aggregation, and is important in outside-in GP IIb-IIIa signaling platelets. This type of signaling is

required for platelet functions such as the formation of platelet aggregates. See p. 14 of the specification.

Accordingly, in view of the teachings of the specification with regard to the specific phenotype exhibited by the claimed mice (*i.e.*, platelets with reduced or absent phosphorylation of mutant GP IIIa protein) the lack of teachings or guidance provided by the specification with regard to any cells, other than the exemplified platelets, and the importance of GP IIIa phosphorylation in platelet function, would have required undue experimentation for one of skill in the art to make and/or use the claimed mice and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 69 is vague and indefinite. The claim recites that the chimeric mouse has reduced or absent phosphorylation of mutant GP IIIa protein compared to wild-type GP IIIa protein. This is unclear because the chimeric mouse would have to be compared to another wild-type mouse, or a mouse with wild-type GP IIIa protein. The mouse is compared to a protein in the claim as written. Claims 70-75 and 92 depend from claim 69.

The prior rejection of claims 70, 73, 77, 80, 84, 89, as vague and indefinite. I maintained. The claims recites that the tyrosine residue is 747 or 759. This is unclear because the numbering of residues would depend upon which sequence (and

whose sequence) the residue would be from. Applicants direct the Examiner to the specification which states that tyrosine 747 and 759 are the tyrosines in the cytoplasmic domain, and to figure 2, which illustrates that. Applicants provide references to a partial mouse GP IIIa amino acid sequence and a complete human sequence, and note that the cytoplasmic domain of the mouse sequence is identical to that of the human sequence. Applicants further provide numerical reference points of nucleotides of the murine GP IIIa gene. See p. 11, 2nd ¶ of the Response. Applicants' arguments are not found to be persuasive. The numbering of residues is relative to where the numbering begins. Merely stating that the residues are 747 and 759 fail to provide a reference point, because these are residue numbers which are dependent upon the particular sequence used.

Claim 76 is vague and indefinite. The claim recites that the transgenic mouse has reduced or absent phosphorylation of mutant GP IIIa protein compared to wild-type GP IIIa protein. This is unclear because the transgenic mouse would have to be compared to another wild-type mouse, or a mouse with wild-type GP IIIa protein. The mouse is compared to a protein in the claim as written. Claims 77-78 depend from claim 76.

The prior rejection of claim 83 as incomplete is maintained. Applicants argue that the claims as amended now provide the step of injecting transformed cells into one or more blastocysts. This is incomplete. It is reiterated that the generation of blastocysts fails to relate to the preamble, a method of preparing a transgenic mouse. Particularly, the mere generation of blastocysts would fail to produce such a

mouse and it would require the introduction of blastocysts into a surrogate mother mouse, the further development of the blastocysts and bringing to term of mice to produce transgenic mice as claimed. Appropriate correction is required. Claims 84-86 depend from claim 83.

Claim 92 recites the limitation "the *transgenic* mouse of claim 69" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 93 is incomplete. The claim recites the determination of the effect of the biological response. This is unclear because it does not relate to the preamble, which states that the biological response is mediated by GP IIIa phosphorylation. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 75 under 35 U.S.C. 102(b) as being anticipated by Zhou *et al.* is maintained for reasons of record.

The claims are directed to platelets isolated from the blood plasma of the chimeric mouse of claim 69.

Applicants argue that Zhou does anticipate the claimed invention because the claims, as amended, now recite that the claimed mouse have reduced or absent

phosphorylation of GP IIIa protein when compared to a wild-type mouse. Applicants point out that while some platelets isolated from the mouse may have the wild-type GP IIIa protein, the mouse, which is the source of the platelets, will have the phenotype of at least reduced phosphorylation of GP IIIa protein, and this phenotype is not taught by Zhou. See p. 12 of the Response.

This is not found to be persuasive. The claims encompass platelets that can be isolated from chimeric, xenograft, or heterozygous mice. If so, some of the platelets that would be isolated could be wild-type platelets. Thus, wild-type platelets are encompassed by the claims. Applicants' arguments are further not persuasive because the claims are directed to the platelets isolated from the chimeric or transgenic mice, not the mice themselves. The phenotypes of the mice do not impart a phenotype on the platelets because the breadth of the claims encompasses isolation of wild-type mouse platelets.

Zhou teach that 700 to 900 μL of whole blood was collected from wild-type mice and platelets were isolated and counted. See p. 1552, 2nd column, *Mouse platelet aggregometry*. As such, the mouse platelets as taught by Zhou anticipate the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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